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# New and Emerging Water Pollutants arising from Agriculture



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# **New and Emerging Water Pollutants arising from Agriculture**

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## *Note*

This document, *New and Emerging Water Pollutants arising from Agriculture*, by the consultant, Alistair B.A. Boxall (Environment Department, University of York, United Kingdom), is one of the background reports supporting the OECD study (2012) *Water Quality and Agriculture: Meeting the Policy Challenge*, which is available at [www.oecd.org/agriculture/water](http://www.oecd.org/agriculture/water).

The report was carried out under the auspices of the OECD Joint Working Party on Agriculture and the Environment of the Committee for Agriculture and the Environment Policy Committee.

**The report is published on the responsibility of the author and does not necessarily reflect the views of the OECD or its member countries.**

The other background reports (also available at [www.oecd.org/agriculture/water](http://www.oecd.org/agriculture/water)) are:

*Water Quality Trading in Agriculture*

James Shortle, Environmental and Natural Resources Institute, Penn State University, United States;

*Agriculture and Water Quality: Monetary Costs and Benefits across OECD Countries*

Andrew Moxey, Pareto Consulting, Edinburgh, Scotland, United Kingdom, assisted by Eva Panagiotopoulou, Department of Agricultural Economics and Rural Development, Agricultural University of Athens, Greece;

*Agriculture's Impact on Aquaculture: Hypoxia and Eutrophication in Marine Waters*

Robert Díaz, Institute of Marine Sciences, United States; Nancy N. Rabalais, Louisiana Universities Marine Consortium, United States and Denise Breitburg, Smithsonian Environmental Research Center, United States. This paper has also been published in OECD (2010) *Advancing the Aquaculture Agenda: Workshop Proceedings*.

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## EXECUTIVE SUMMARY

- In recent years, there has been increasing concern over the environmental risks of the so called 'emerging contaminants' (ECs). ECs originate from a variety of product types including human pharmaceuticals, veterinary medicines, nanomaterials, personal care products, paints and coatings. Some ECs, such as natural products and transformation products of synthetic chemicals may be formed in the environment by biochemical processes in animals, plants and microbes. Environmental risk assessment schemes already exist in certain regions for these substances.
- ECs are not necessarily new chemicals; they may be substances that have been present in the environment for a long time but whose presence and significance are only now being recognised. Data for ECs are often scarce and methods for detection in the natural environment may be non-existent or at an early stage of development. For some classes of ECs, existing environmental assessment methods (e.g. exposure models and fate and effects test approaches), may not be appropriate.
- ECs will be released to the agricultural environment via a number of routes. They may be released directly to the environment (e.g. veterinary medicines that are used to treat animals at pasture). They may also enter the environment indirectly during the application of manure, biosolids or other solid waste materials to soil. Once in soil ECs may be transported to water bodies by leaching, runoff and drainage processes. The extent of the transport is dependent on the persistence of the EC and on how it interacts with soil and sediment particles.
- ECs will also be released to the aquatic environment from non-agricultural sources (e.g. emissions from wastewater treatment plants). For some classes of ECs (e.g. human medicines and human personal care products), emissions from these other sources are likely to be more significant than emissions from agriculture. For veterinary medicines, hormones, selected transformation products and natural toxins, agriculture is the most significant source of water contamination.
- Many ECs appear to behave differently in environmental systems than other agricultural contaminants (such as traditional pesticide active ingredients and persistent organic pollutants). This means that modelling approaches that have been developed for predicting fate properties and exposure of other contaminants are not always appropriate for ECs.
- Detection of ECs in environmental media can be challenging. However, robust methods are now available for many ECs, including selected human and veterinary medicines, personal care products, and transformation products of synthetic chemicals. Methods are currently poorly developed for the detection and characterisation of engineered nanoparticles in soils and natural waters.
- While a large number of studies have investigated the occurrence of a wide range of ECs across the globe, only a few studies have specifically investigated occurrence of ECs in agricultural systems. The studies that have looked at agricultural systems have detected a range of ECs including veterinary drugs, human pharmaceuticals, personal care products, hormones and transformation products of man-made chemicals. Generally, reported concentrations are very low (i.e. in the ng/l range).



- Most ECs cause acute toxicity at high concentrations. These concentrations are typically much higher than concentrations measured in the environment indicating that ECs are unlikely to cause acute effects on organisms in the systems where the monitoring has been done.
- A range of non-standard effects have been reported for different ECs, in particular for ECs that are designed to be biologically active (e.g. veterinary and human medicines). These effects are often seen at concentration levels close to those measured in the environment. However, the implications of these effects in terms of ecosystem functioning have yet to be established.
- The environment will be exposed to a mixture of ECs and other contaminants. The impact of these mixtures is likely to be greater than the impact of the single substances on their own. It is therefore important that we begin to consider the potential implications of these mixture interactions in terms of risk. This is a general problem that is also relevant to non emerging contaminants such as pesticides, persistent organic pollutants and heavy metals.
- New ECs are likely to emerge in the future due to technological developments and changes in demographics, society, land-use and climate. It is important that we begin to develop ‘horizon-scanning’ approaches to anticipate these changes.
- It is important that we work to identify ECs of most concern so that resources can be focused on the bigger problems. A number of prioritisation approaches already exist for horizon scanning for different classes of ECs. However, these approaches need further development and need to be applied more widely. In order to co-ordinate resources, it may be appropriate to establish an international watchdog on EC’s or to promote greater international cooperation.

## NEW AND EMERGING WATER POLLUTANTS ARISING FROM AGRICULTURE

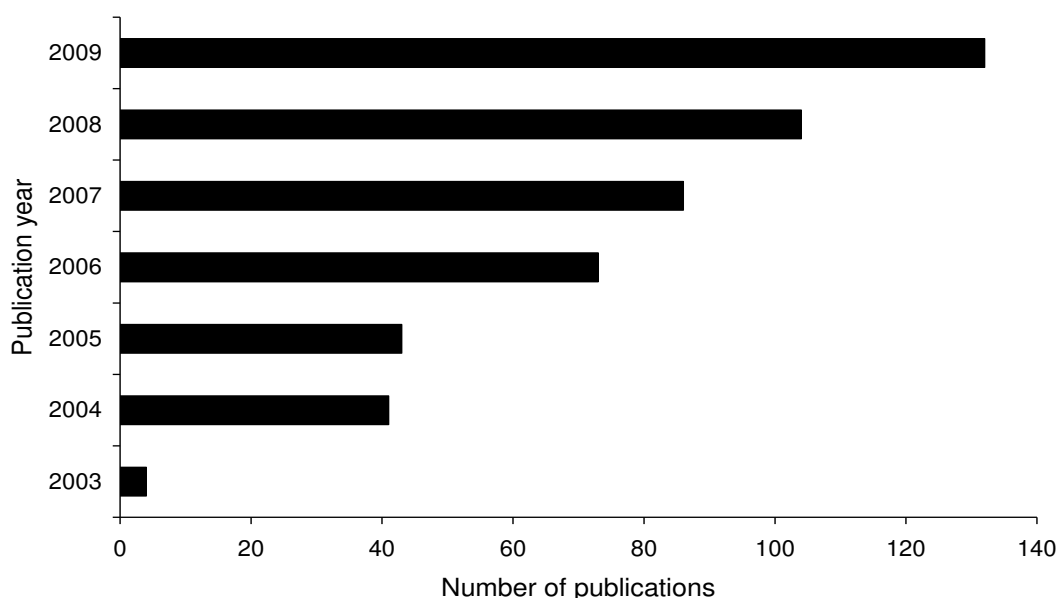
by

Alistair B.A. Boxall<sup>1</sup>

### 1. Introduction

Until very recently, the main focus on the impacts that chemicals cause in the environment has been on nutrients heavy metals, ‘traditional’ active ingredients in pesticide products and persistent organic pollutants. However, in recent years, there has been increasing concern over the environmental risks of the so called ‘emerging contaminants’ (ECs). ECs originate from a variety of product types including human pharmaceuticals, veterinary medicines, nanomaterials, personal care products, paints and coatings. Some ECs, such as the natural toxins and degradation products of man-made chemicals may also be formed within the natural environment by animals, plants and microbes. The increasing concern over the risks of ECs is reflected by a rapid increase in the numbers of scientific publications exploring the environmental impacts of ECs over the past decade (Figure 1) and the appearance of numerous articles in the popular press across the world.

**Figure 1. Numbers of publications with the words ‘emerging contaminants’ and ‘environment’ in the title or abstract published since 2003**



Source: Taken from Web of Science.

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1. EcoChemistry Research Group, Environment Department, University of York, Heslington, York, United Kingdom.

Numerous classes of ECs have been shown to be released to the environment, or in the case of nanomaterials, will be released to the environment in increasing amounts in the future. In the environmental monitoring studies that have looked for them, EC's have been detected in a range of environmental compartments including surface waters, groundwaters, drinking waters, fish and earthworms across the globe (e.g. Kolpin *et al.*, 2002, Juhler *et al.*, 2001; Ferrer *et al.*, 2000; Kolpin *et al.*, 1998a and b; Schnoebelen *et al.*, 2001; Battaglin *et al.*, 2003; Li *et al.*, 2002; Zimmerman *et al.*, 2002; Lagana *et al.*, 2002).

Alongside the monitoring, studies have been performed to explore the effects of a range of ECs on the biochemistry, cell structure, growth, reproduction and mortality of organisms in the environment and on populations and communities in surface water and soil systems. While much of the data that has been produced on different classes of ECs indicates that many pose a small risk to ecosystems and human health there is some evidence that selected emerging contaminants could affect human and environmental health. For example, the veterinary use of diclofenac, which is a human pharmaceutical used as an anti-inflammatory treatment, was found to be responsible for the massive decline in populations of vulture species in certain areas of Asia (Oaks *et al.*, 2004); the veterinary drug ivermectin, which is used to treat parasitic infections in livestock, has been shown to affect the growth of aquatic invertebrates at concentration lower than those that are expected to occur in the aquatic environment (Garrić *et al.*, 2007); ethinylestradiol, one of the active ingredients in the contraceptive pill, has been associated with endocrine disruption in fish (Lange *et al.*, 2001); and there is concern that long-term exposure to antibiotic pharmaceuticals, used in human and veterinary medicine, may be contributing to the selection of resistant bacteria in the environment which may have significant implications for human health (Boxall *et al.*, 2003a).

This paper provides an overview of those ECs that have an agricultural-based origin or which may be released to agricultural systems, which may be of concern to water quality. The first section defines what an EC is. Subsequent sections then discuss the potential inputs, fate and transport, effects and risks of ECs in agricultural systems. An overview of existing regulatory systems that cover ECs is provided and possible prioritization approaches for identifying those ECs that are likely to pose the greatest risk to human health and the environment are discussed. Finally, recommendations on future research priorities are given.

## **2. What is an emerging contaminant?**

ECs are not necessarily new chemicals; they may be substances that have been present in the environment for a long time but whose presence and significance are only now being recognised. Data for ECs are often scarce and methods for detection in the natural environment may be non-existent or at an early stage of development. There is no internationally agreed definition for an emerging contaminant and a number of definitions have been proposed (Box 1). Many of these definitions are contradictory and could apply to many of the environmental contaminants that we have been studying for many years.

I would advocate that an 'emerging contaminant' is 'a contaminant from a chemical class that so far has not been studied extensively, where there is either a concern from stakeholders (scientists, regulators, NGOs etc.), that the contaminant class may be having an impact on environmental or human health; or where there is a concern that existing environmental assessment paradigms are not appropriate for the contaminant class'.

#### **Box 4. Definitions of 'emerging contaminants' in different regions/sectors**

"Substances that have been detected in the environment, but which are currently not included in routine monitoring programmes at EU level and whose fate, behaviour and (eco)toxicological effects are not well understood." (definition of the EU NORMAN network)

"Those chemicals that recently have been shown to occur widely in water resources and identified as being a potential environmental or public health risk, and yet adequate data do not exist to determine their risk." (definition of the Consortium for Research and Education on Emerging Contaminants)

"Hazardous materials (chemical, microbial or radiological substances) or mixtures of interest that are characterized by: a perceived or real threat to human health, public safety or environment; no currently published health standard/guideline exists or it is evolving or being re-evaluated; there is insufficient or limited available toxicological information; or, a new source, pathway, or detection limit has been discovered. Emerging contaminants may be naturally occurring or manmade." (definition of the State of Massachusetts)

"Contaminants with a potential threat to health and environment that have no regulatory standard." (definition of the State of South Carolina)

"A chemical or material that has pathways to enter the environment and presents potential unacceptable human health or environmental risks, and either does not have regulatory peer-reviewed human health standards or the regulatory standards are evolving due to science, detection capabilities, or new pathways." (definition of Chemical Material Risk Management)

"Any synthetic or naturally occurring chemical or any microorganism that is not commonly monitored in the environment but has the potential to enter the environment and cause known or suspected adverse ecological and/or human health effects. In some cases, release of emerging chemical or microbial contaminants to the environment has likely occurred for a long time, but may not have been recognized until new detection methods were developed. In other cases, synthesis of new chemicals or changes in use and disposal of existing chemicals can create new sources of emerging contaminants." (definition of the US Geological Survey)

ECs arise from a plethora of product types and cover a wide range of chemical classes. In terms of agricultural systems, there are a number of EC types of potential concern, including:

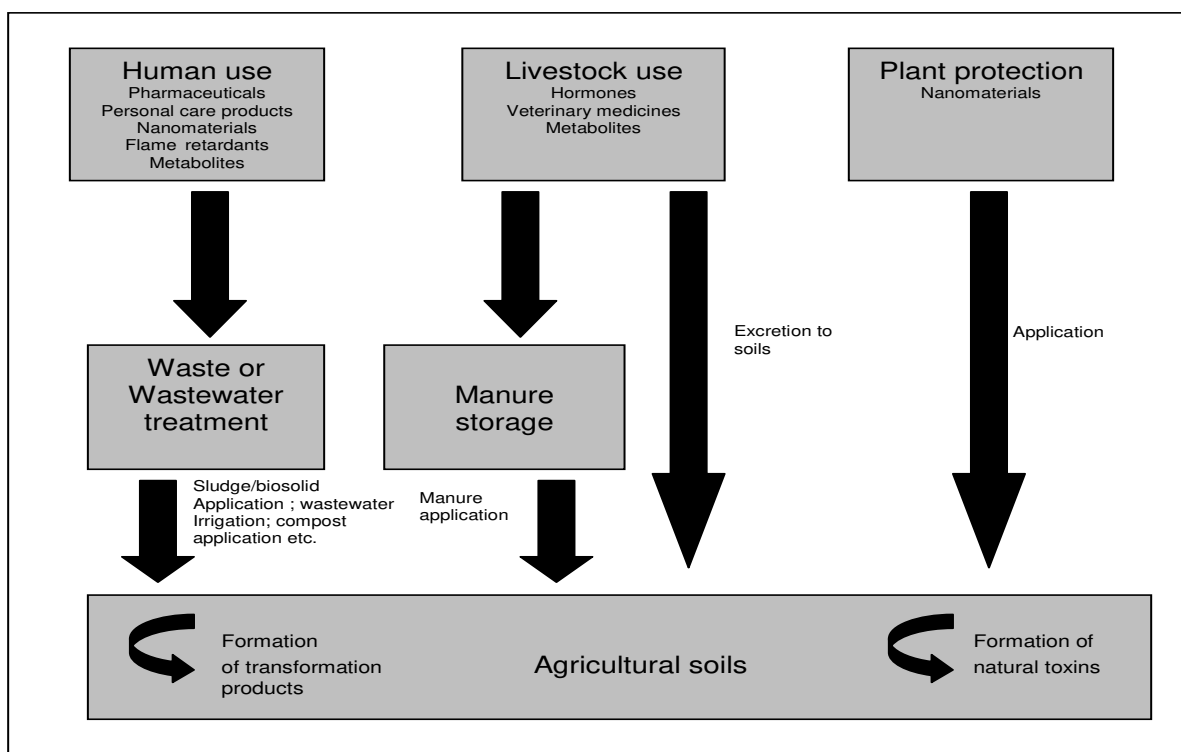
- Naturally produced compounds such as toxins produced by fungi, bacteria and plants;
- Bio-terrorism/sabotage agents;
- Human personal care products such as essential oils, herbal medicines, antibacterials and fragrances;
- Emerging persistent organic pollutants such as flame retardants and dioxin-like compounds;
- Veterinary medicines such as antibiotics and antiparasitic agents;
- Hormones such as synthetic and natural estrogens and androgens;
- Nanomaterials;
- Human medicines;
- Metabolites and transformation products of man-made chemicals that are produced from biological, chemical and physical breakdown reactions.

A detailed list of EC classes along with example substances is available on the EU NORMAN network website ([www.norman-network.net](http://www.norman-network.net)).

### 3. Sources of emerging contaminants into the agricultural environment

ECs will be released to the agricultural environment via a number of routes (Figure 2). Veterinary medicines and their metabolites will be released directly to soils (animals at pasture) or indirectly when manure and slurry from intensive livestock facilities is applied to agricultural land as a fertiliser (Boxall *et al.*, 2004a). Human pharmaceuticals and personal care products will be released through the application of sewage sludge (biosolids) to land or from irrigation with wastewater effluent. Other ECs may be formed in the environment itself. Detailed examples are provided below.

Figure 2. Routes of entry of ECs to the agricultural environment



Source: Author.

New ECs may also be added intentionally to agricultural systems in the future. For example, it is likely that pesticides may increasingly be applied in the nano-scale (i.e. as particles in the size range 1-100 nm; Lyons and Scrinis, 2009). Existing pesticides may be made in the nanoparticulate form to give the active ingredient beneficial properties for pest control, such as increased solubility, increased stability, the capacity for absorption into plants or increased toxicity to pests (Lyons and Scrinis, 2009). Pesticides may also be nano-encapsulated to create nano-scale capsules, which can be designed, for example, to release the pesticide in specific environments, such as inside the stomach of an insect. These 'smart' pesticides could provide more precise, controlled and effective use of pesticides, and therefore potentially reduce the overall quantities of pesticide used (Lyons and Scrinis, 2009).

ECs may also be created in the agricultural environment itself. Many man-made substances that enter agricultural systems will be degraded by chemical, physical and biological processes. While these reactions may result in the complete breakdown of a chemical (i.e. they convert the chemical to carbon dioxide, water and methane), in many instances the processes may result in the formation of stable intermediate chemicals which we call degradation or transformation products (e.g. Roberts,

1998, Roberts and Hutson, 1999). Many ECs are also produced naturally by fungi, bacteria, algae, plants, and animals. According to their origin, these toxins are usually separated into the categories: mycotoxins (fungal origin), bacterial toxins (bacterial origin), phycotoxins (algal origin), phytotoxins (plant origin), and zootoxins (animal origin) (van Egmond, 2004). These are usually produced by the organisms as a defence mechanism.

While human pharmaceuticals, personal care products and other ECs originating from households, towns and cities are not applied directly to agricultural systems, they are able to enter the agricultural environment indirectly. Following use, many of these ECs will be released to the wastewater system. Typical wastewater systems involve a primary treatment phase, where solid material is settled out and removed, followed by a secondary treatment where microbes are used to breakdown organic matter (including chemicals). One common secondary treatment process is activated sludge treatment (AS). In AS, chemical contaminants may be degraded but can also stick to the sludge particles in the system. At the end of the process, the sludge is removed and, as it is high in nutrients, in many regions is then applied to agricultural land as a fertiliser. ECs that stick to sludge can therefore enter the environment when sludge (biosolids) from wastewater treatment works is applied to land (Kinney *et al.*, 2006; Topp *et al.*, 2008a).

#### **4. The significance of agriculture as a source of ECs**

As discussed above, ECs originate from a wide range of sources and, in some instances, inputs to surface waters from agricultural activities may be insignificant compared to other sources. For example, agricultural inputs of ECs from human medicines and personal care products into the aquatic environment are probably less important than other routes of entry into the natural environment. These products are typically used by society all the time and therefore emitted continuously from wastewater treatment systems into the aquatic environment whereas sludge application to land will tend to happen only at certain times of year. Therefore, pharmaceuticals and personal care products are likely to occur sporadically in agricultural waterbodies. The actual concentrations of pharmaceuticals and personal care products transported from agricultural soils to surface waters are also much lower than seen in sewage effluent (Topp *et al.*, 2008).

The ECs where agriculture is currently the predominant source of surface water contamination, compared to non-agricultural sources, are the natural toxins, veterinary medicines, hormones and transformation products of man-made chemicals used in agriculture. For some ECs, agriculture might be an important source of contamination in the future. For example, if pesticides are developed in the nano-form in the future, it is likely that these materials will be transported to and contaminate surface waters. For some ECs, e.g. bioterrorism/sabotage agents, the importance of agriculture as a source of contamination is difficult to predict.

The potential routes of input of different classes of ECs to surface waters are summarised in Table 1. The table also provides an indication of the relative importance of agricultural releases compared to other sources. It is important to recognise that the relative importance of the different source may vary according to regional differences in e.g. farming and wastewater treatment practices and to differences in the physical and chemical properties of individual ECs within a class.

**Table 1. Routes of input of ECs to surface waters and the importance of agricultural inputs compared to other sources**

<b>Emerging contaminant class</b>	<b>Route of input to agricultural systems</b>	<b>Other sources to the environment</b>	<b>Relative importance of agricultural sources in terms of water contamination</b>
Natural toxins	Release from plants, algae and fungi	NA	High
Veterinary medicine	Direct release to soils from animals at pasture; application of contaminated manure and slurry to land	Use in aquaculture; manufacturing releases; disposal of containers	High
Hormones	Direct release of natural and synthetic hormones by animals at pasture; application of manure and slurry to land	Application of sewage sludge, containing natural and synthetic hormones arising from the human population	High – hormonal substances arising from animals Low – hormonal substances arising from the human population
Transformation products	Produced from man made chemicals that are applied directly to agricultural systems or in activated sludge/irrigation water	Formed in wastewater treatment processes	Dependent on the nature of the parent compound: High (TPs of veterinary medicines) Low (TPs of pharmaceuticals, personal care products etc.)
Nanomaterials	Application of nanopesticides to crops; release of nanomedicines by livestock; application of sewage sludge to agricultural land as a fertiliser; irrigation with wastewater or contaminated surface water	Emissions from wastewater treatment plants; disposal of waste to landfill; manufacturing releases	Currently low as nanomaterials are mainly used in personal care products and paints and coatings  Importance could increase in the future as the nanopesticide and nanomedicine markets develop.
Bioterrorism/sabotage agents	Sabotage of crops and livestock	Chemical incidents in cities	Has the potential to be high (depending on the agent)
Human personal care products	Application of sewage sludge to agricultural land as a fertiliser; irrigation with wastewater or contaminated surface water	Emissions to surface waters from wastewater treatment plants	Low

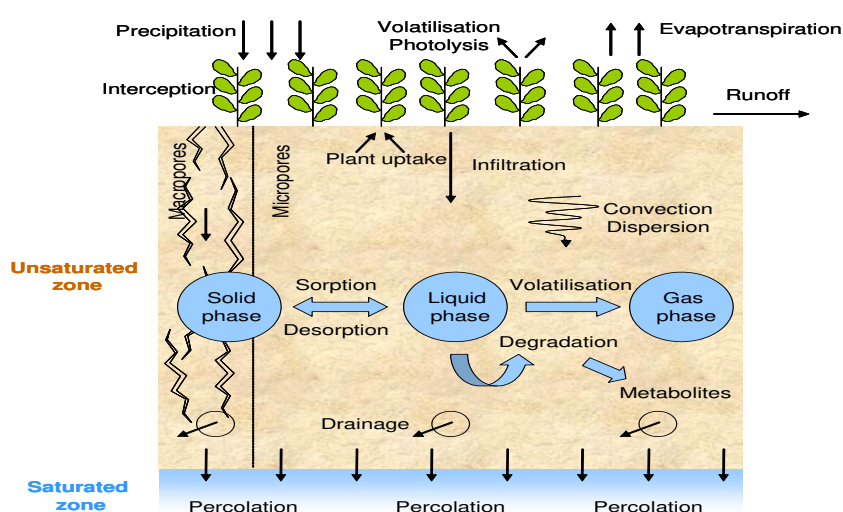
**Table 1. (continued) Routes of input of ECs to surface waters and the importance of agricultural inputs compared to other sources**

Emerging contaminant class	Route of input to agricultural systems	Other sources to the environment	Relative importance of agricultural sources in terms of water contamination
Emerging persistent organic pollutants (e.g. flame retardants)	Application of sewage sludge to agricultural land as a fertiliser; irrigation with wastewater or contaminated surface water	Emissions to surface waters from wastewater treatment plants	Low
Human medicines	Application of sewage sludge to agricultural land as a fertiliser; irrigation with wastewater or contaminated surface water	Emissions from wastewater treatment plants; disposal of unused medicines to landfill; manufacturing releases	Low

## 5. Fate and transport of ECs in agricultural systems

Once an EC is released to or formed in the agricultural environment, it will experience the same fate and transport processes that occur for other classes of agricultural contaminant (Figure 3). The EC may be degraded by biological, physical or chemical processes, it may stick to soil particles, it may be taken up by plants, it may leach to groundwater or it may be transported to surface waters through runoff and drainage water. The extent to which any of these processes happens will depend on the underlying physical properties of the EC (including how soluble it is in water solubility; how attracted the EC is to organic matter and other soil components; and how volatile the substance is) as well as the properties of the soil and the climatic conditions. In the following sections information on the fate and transport of emerging contaminants in the environment is reviewed.

**Figure 3. Fate and transport processes for contaminants in the agricultural soil environment**



Source: Author.



## 5.1 Sorption in soil

When applied to a field, chemicals may associate with soil particles by attaching to the surface of the soil and/or moving inside the soil particle. This process is known as sorption and is a very important factor in determining whether a chemical is going to move to surface waters and groundwaters or not, it also affects the degradation of a chemical. For pesticides and the persistent organic pollutants, our understanding of sorption behaviour in soils is well developed due to significant research over the years. These contaminants typically interact with the organic carbon in the soil and sorption behaviour can be predicted from a knowledge of the hydrophobicity (which is a measure of the attractiveness of the contaminant to organic material) of the chemical. Equations exist for estimating the sorption behaviour of a chemical in soils based on the hydrophobicity of the chemical and the total organic carbon content of the soil and these are routinely used in environmental exposure modelling and environmental risk assessment. While, these equations are probably valid for many ECs, many other ECs, including the human and veterinary medicines and engineered nanomaterials, appear to behave differently.

The sorption behaviour of human and veterinary medicines can vary vastly in different soil types and these differences in sorption of a given compound in different soils cannot be explained by variations in soil organic carbon but are explained by the fact that many pharmaceuticals are polar meaning that they can exist in natural environments in both the unionized and ionized form (e.g. Ter Laak *et al.*, 2006a and b). As a result, the chemicals do not just interact with the organic carbon in the soil but also with other soil components such as metal oxides and clay particles (Ter Laak *et al.*, 2006b) and the sorption behaviour is very dependent on properties of the soil, such as soil pH. The complexities of these interactions means that modelling approaches, developed for predicting the sorption of other groups of chemicals (e.g. pesticides and neutral organics), are inappropriate for use on many human and veterinary medicines. Great care should therefore be taken when using existing modelling and risk assessment approaches, developed for 'traditional' chemical classes, to ECs.

Many ECs will also enter the agricultural environment associated with manure and slurry and these matrices may also alter the behaviour and transport of ECs. Studies have demonstrated that the addition of manure or sludge can affect the sorption behaviour of veterinary and human medicines and personal care products and that they may also affect persistence (e.g. Boxall *et al.*, 2002; Thiele Bruhn and Aust, 2004; Monteiro and Boxall., 2009; Topp *et al.*, 2008b; Al Rajab *et al.*, 2009). In some cases, the addition of the sludge or manure increases sorption and persistence and in other cases, they decrease sorption and persistence. These effects have been attributed to changes in pH or alterations of the nature of dissolved organic carbon in the soil/manure system.

Very few studies have explored the interaction of engineered nanoparticles with soil particles (e.g. Li *et al.*, 2008). However, based on information for other processes, it is likely that the behaviour of these materials will be different from non-particulate contaminants and that new models and paradigms will need to be developed for engineered nanoparticles in the soil environment.

## 5.2 Persistence in soil

Like other contaminants, the main route for degradation of ECs in soils will be via aerobic (i.e. in an oxygen containing environment) biodegradation. Depending on the nature of the chemical, other degradation and depletion mechanisms may occur, including soil photolysis (caused by sunlight) and hydrolysis (caused by a reaction with water) (e.g. Wolters and Steffens, 2005). Most data on the persistence of ECs in soil are for veterinary and human medicines, personal care products and transformation products of pesticides and data on the persistence of these classes of ECs needs to be generated as part of the regulatory risk assessment processes for these products.

Like, sorption, the presence of the biosolid or sludge matrix seems to affect degradation rates compared to soil on its own. For example, for caffeine which not only arises from coffee consumption but also is used as a pharmaceutical, degradation rates in soils increased with addition of aerobically-digested sewage sludge. In contrast, anaerobically-treated (i.e. treated in a low oxygen environment) sewage sludge did not accelerate caffeine mineralization (Topp *et al.*, 2006). The degradation rate of the human pharmaceutical naproxen, an anti-inflammatory treatment, was also reported to be increased by the addition of activated sludge (Topp *et al.*, 2008b).

When assessing degradation in the laboratory, scientists typically look at the disappearance of the study compound using analytical extraction and detection techniques and also attempt to identify the transformation products and whether the compound is completely mineralized (i.e. degraded to carbon dioxide and water). In only a few published studies has the formation of degradation products of ECs been investigated (Kolz *et al.*, 2005; Topp *et al.*, 2008b). In these studies, no detectable transformation products were found for naproxen or the hormones estrone and 17 $\beta$ -estradiol (Topp *et al.*, 2008b). While some of the compounds are extensively mineralized, others are not yet the parent compound still disappears. One possible explanation for this is that the parent EC is binding very tightly to the soil particle and that this cannot be extracted by the analytical methods used in the degradation study. This phenomenon has also been observed for some pesticides and the fraction that cannot be extracted is termed the 'non-extractable residue' (NER). There is currently considerable discussion, particularly in Europe, over how to deal with NERs in the environmental risk assessment process. Many people argue that NERs cannot be ignored as it is possible that they could be 'mobilised' at a later date due to changes in soil conditions.

We know very little about the persistence of engineered nanomaterials in agricultural soils. Nanomaterials are likely to dissipate via different pathways than traditional chemicals. For example, the particles may aggregate or agglomerate which will alter the properties of the particle and some nanomaterials may undergo dissolution. Many nanomaterials are likely to be capped with organic molecules, it is possible that these cappings will be degraded by microbes or abiotic processes. To understand the behaviour of nanomaterials in agricultural systems, it is likely that we will need to begin to develop an understanding of all of these different pathways of dissipation.

### **5.3      *Transport in soil systems***

Contaminants applied to or formed in soil can be transported to aquatic systems in surface runoff, subsurface flow and drainflow. The extent of transport via any of these processes is determined by a range of factors, including: the solubility, sorption behaviour and persistence of the contaminant; the physical structure, pH, organic carbon content and cation exchange capacity of the soil matrix, and climatic conditions such as temperature and rainfall volume and intensity. Most work to date on contaminant transport from agricultural fields has focused on pesticides, nutrients and bacteria, but recently a number of studies have explored the fate and transport of ECs. Lysimeter (which is an intact and undisturbed soil column), field-plot and full-scale field studies have investigated the transport of veterinary medicines and pharmaceuticals and personal care products from the soil surface to field drains, ditches, streams, rivers and groundwater (e.g. Blackwell *et al.*, 2007 and 2009; Kay *et al.*, 2004; 2005 a,b and c; Aga *et al.*, 2003; Kreuzig and Holtge, 2005; Burkhard *et al.*, 2005; Hamscher *et al.*, 2005; Chefetz *et al.*, 2008; Topp *et al.*, 2008a; Lapen *et al.*, 2008). A range of experimental designs and sampling methodologies has been used. These investigations are described in more detail below.

### 5.3.1 Leaching to groundwater

A series of studies have explored the potential for ECs to leach from soils to groundwaters. These have involved laboratory column studies, lysimeter studies and full-scale field investigations. Oppel *et al.* (2004) used laboratory column studies to assess the potential for six pharmaceuticals to move from field surfaces to groundwaters. While the majority of the pharmaceuticals were found not to leach, two (clofibric acid and iopromide) were very mobile under the experimental conditions and thus, groundwater contamination would be possible if the soil is exposed to these pharmaceuticals,

The movement of veterinary antibiotics from the sulfonamide and tetracycline groups, which are three of the most widely used classes of antibiotic in the world, in soil profiles has been investigated at the field scale using suction probes (Blackwell *et al.*, 2007; Hamscher *et al.*, 2000). In these studies, sulfonamide antibiotics were found at depth but the tetracyclines were not; most likely due to the high potential for tetracyclines to sorb to soil. Carlson and Mabury (2006) reported that chlortetracycline applied to agricultural soil in manure was detected at soil depths of 25 and 35 cm, but monensin, a coccidiostat, remained in the upper soil layers.

There are only a few reports of veterinary medicines in groundwater (Hamscher *et al.*, 2000; Hirsch *et al.*, 1999). Residues of sulfonamide antibiotics were detected at a few of the study sites investigated by Hirsch *et al.* (1999) in Germany. Contamination at two of these sites was attributed to irrigation of agricultural land with domestic sewage but the other sites were believed to have become contaminated due to the application of animal manures to the soil surface (Hirsch *et al.*, 1999).

### 5.3.2 Runoff

Transport of ECs via runoff (i.e. overland flow) has been observed for tetracycline antibiotics, sulfonamide antibiotics, anti-inflammatory agents, antiepileptic compounds, beta blockers, antidepressants, triclosan (an antibacterial compound used in toothpaste and chopping boards) and caffeine (Kay *et al.*, 2005; Kreuzig *et al.*, 2005b; Topp *et al.*, 2008). Just like leaching, the transport of these substances is influenced by the sorption behaviour of the compounds, the presence of manure or sludge in the soil matrix and the nature of the land to which the manure or sludge is applied. Runoff of highly sorptive substances, such as tetracyclines, was observed to be significantly lower than the more mobile sulfonamides (Kay *et al.*, 2005). However, even for the relatively water soluble sulfonamides, total mass losses to surface are very small (with less than 0.6% of the mass applied being transported to surface waters) under actual field conditions (Stoob *et al.*, 2007). Manure and slurry has been shown to increase the transport of sulfonamides via runoff by 10-40times in comparison to runoff following direct application of these medicines to soils (Burkhard *et al.*, 2005). Possible explanations for this observation include physical “sealing” of the soil surface by the slurry and/or a change in pH as a result of manure addition that alters the speciation and fate of the medicines (Burkhard *et al.*, 2005). It has been shown that overland transport from ploughed soils is significantly lower than runoff from grasslands (Kreuzig *et al.*, 2005b). The application method can also influence the runoff behaviour of ECs, for example Topp *et al.*, (2008) showed that application of sewage sludge by injection greatly reduced the runoff of a range of pharmaceuticals. The way in which the agricultural land is managed therefore seems to have a significant impact on the transport of ECs to surface waters and it is possible, that changes in land management practices could offer a management solution in the event that an EC is found to cause impacts in agricultural systems.

### 5.3.3 Drain flow

The transport of a range of veterinary antibacterial substance (i.e. tetracyclines, macrolides, sulfonamides and trimethoprim (a veterinary drug that is often used in combination with sulfonamide antibiotics) has been investigated using lysimeter and field-based studies in tile-drained clay soils (Boxall *et al.*, 2006; Kay *et al.*, 2004). Following application of pig slurry spiked with oxytetracycline and sulfachloropyridazine, the test compounds were detected in drainflow water (Kay *et al.*, 2004). Concentrations of the sulfonamide were an order of magnitude higher than the tetracycline even though the amount of each test compound applied to the field was similar, these difference are again likely due to differences in sorption behaviour. In a subsequent investigation at the same site (Kay *et al.*, 2004), in which the soil was tilled, much lower concentrations were observed in the drainflow suggested that tillage may be a useful mitigation strategy in the even that a veterinary product is found to pose a risk to aquatic systems. While the pig slurry used in these studies was obtained from a pig farm where tylosin was used as a prophylactic treatment, this substance was not detected in any drainflow samples; possibly because it is not persistent in slurry (Loke *et al.*, 2000).

Similar studies have been done on human pharmaceuticals in tile drain water from sludge-amended fields (Lapen *et al.*, 2008 and 2009). A range of pharmaceuticals and personal care products were observed in the drainage waters including naproxen, acetaminophen, ibuprofen, cotinine, carbamazepine, triclosan, atenolol, triclocarban, gemfibrozil. The observed concentrations were significantly lower than those observed in wastewater effluents.

### 5.4 Surface waters

In the water column, substances may be degraded abiotically via photodegradation and/or hydrolysis or biotically by aerobic or anaerobic organisms. Highly sorptive substance may partition to the bed sediment. For example, mesocosm studies using ivermectin show that when added to water, the compound dissipates quickly from the water column and that this dissipation is observed increase in the concentration of the compound in the bed sediment (e.g. Sanderson *et al.*, 2007). A significant amount of information is available on the fate and behaviour of many veterinary medicines in water-sediment systems due to the use of veterinary medicines as aquaculture treatments (Boxall *et al.*, 2004). For selected new human pharmaceuticals, companies are required to test the fate of the compound in a laboratory sediment-water system so an increasing amount of information is becoming available for these substances. While many compounds degrade very quickly, others persist in the sediment for months to years.

### 5.5 Uptake into biota

ECs may also be taken up from soil into biota (Migliore *et al.*, 2003; Kumar *et al.*, 2005; Boxall *et al.*, 2006; Dolliver *et al.*, 2007). The potential uptake of veterinary and human medicines into plants is receiving increasing attention. Studies with a range of veterinary medicines (Boxall *et al.*, 2006) showed that a number of antibiotics are taken up by plants following exposure to soil at environmentally-realistic concentrations of the compounds whereas other compounds were not observed to be accumulated. Less work has been done on human pharmaceuticals but recent studies have shown that the antidepressant compound fluoxetine be accumulated by brassicas (Redshaw *et al.*, 2008). The factors affecting uptake of ECs into plants are poorly understood and this is an area that needs much more research. Recently, the uptake of ECs into other soil organisms has also been explored, for example Kinney *et al.* (2008) reported the occurrence of anthropogenic waste indicators, including the pharmaceutical trimethoprim in earthworm tissue.

## 6. Occurrence of emerging contaminants in soils, surface waters and groundwaters

The detection of ECs in the environment can be highly challenging as they typically occur in the environment at very low levels and, for many ECs, reference standards, which are required to validate the analytical methods, are not available. Analysis is also very time consuming and costly and requires access to highly sophisticated equipment. Robust methods are however now available for detecting many emerging contaminants (e.g. pharmaceuticals, personal care products, veterinary medicines and transformation products) in waters, soils and sediments. While many of these methods cannot yet be regarded as 'routine', they are beginning to be used in numerous laboratories around the world. For some ECs, such as the engineered nanomaterials, detection in the environment is still not currently possible due to a lack of sensitive techniques for detection and characterization of these materials in complex matrices (Tiede *et al.*, 2008). The analysis of many nanomaterials in environmental samples is further complicated that waters and soils already contain numerous natural nanoparticles – one of the major challenges is how we distinguish between natural and man-made materials.

Nevertheless, availability of liquid chromatography-mass spectrometry analytical techniques has allowed us to study the occurrence and fate of many ECs in environmental systems. The focus of the analytical work has been on detection of ECs in surface waters and wastewater effluents (Ternes, 2001; Heberer, 2002; Benotti *et al.*, 2009) with less work being done on soils, groundwaters and only a few studies exploring detection in other biological environmental matrices such as vertebrate, invertebrate and plant material (Brooks *et al.*, 2005; Ramirez *et al.*, 2009). The surface water monitoring studies tend to look at sites where the ECs are being released from a range of sources, including wastewater emissions, it is therefore often difficult to determine whether an EC is of agricultural origin or not.

A few studies have however focused on detection of ECs in agricultural catchments. These investigations have detected a range of pharmaceuticals, veterinary medicines, personal care products hormones and transformation products across a number of countries in N. America, Asia and Europe (Table 2). While concentrations are generally low (i.e. in the ng/l range), many ECs have been detected throughout the year.

**Table 2. Emerging contaminants detected in runoff and drainage waters, surface waters or groundwaters associated with agricultural land**

EC class	Product class	Countries where the EC class has been monitored and detected
<b>Veterinary medicines</b>	Antibiotics	Canada, United States, United Kingdom, Japan, China, Korea Luxembourg, Switzerland, Chinese Taipei
	Antiparasitic agents Ionophores	United Kingdom, Canada Canada, United States, Denmark
<b>Human medicines</b>	Analgesics	Canada
	Antibiotics	Switzerland
	NSAIDs	Canada
	$\beta$ -blockers	Canada
<b>Human personal care products</b>	Antibacterials	Canada, United States
	Insect repellants	United States
	Polycyclic musks	United States
<b>Hormones</b>	Synthetic estrogens	United States
	Natural estrogens	United States, Chinese Taipei
	Androgens	United States
<b>Transformation products</b>	Transformation products of herbicides	Greece, United States, France, Germany, Switzerland
	Transformation products of pesticides	Canada, United States

Source: adapted from reviews by Monteiro and Boxall (2010); Boxall et al. (2010).

## 7. Effects and risks of emerging contaminants on ecosystems and humans

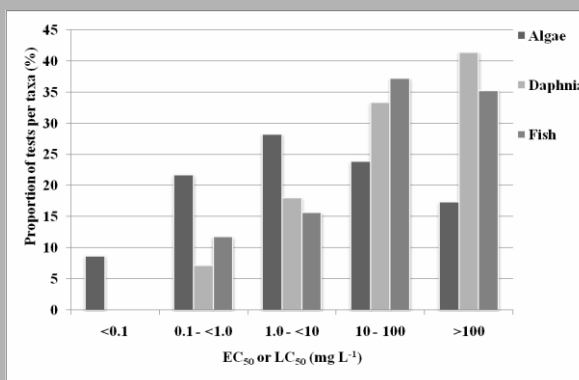
A wealth of research is now being done to assess the effects of emerging contaminants on ecosystems and human health. The following section explores the effects of a range of emerging contaminants. While the examples are not always relevant to the aquatic environment, they do illustrate the potential hazards associated with different classes of EC.

### 7.1 Human and veterinary medicines

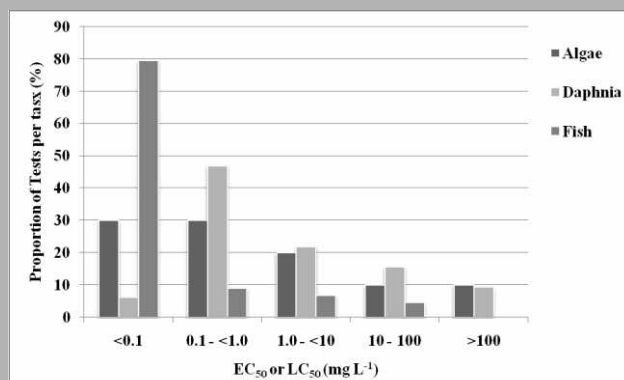
#### 7.1.1 Acute and chronic effects from standard studies

In the EU and North America, the environmental risks of human and veterinary medicines now need to be assessed before a product can be marketed and in order to perform the risk assessment, data are often required on the effects on aquatic and terrestrial organisms (Breton and Boxall, 2003). A reasonable body of data is therefore available on the effects of many medicines on aquatic invertebrates, fish and algae, earthworms, plants and soil microbes (e.g. see Boxall *et al.*, 2004a). These data have generally been obtained using standard acute or chronic ecotoxicity studies. The acute studies are short term (2-4 days) with mortality (fish and invertebrates) or growth (algae) as the endpoint whereas chronic studies last weeks to months and investigate effects on growth and reproduction. Acute effects of pharmaceuticals are observed at concentrations orders of magnitude higher than measured concentration and generally algae are more sensitive in these studies (Box 2). Chronic effects are seen at concentrations much lower than in the acute studies but. As with the acute studies, effects in standard chronic studies are typically seen at concentrations that are much higher than measured concentrations, indicating that levels of pharmaceuticals in the natural environment will not be high enough to cause these effects.

**Box 5. Distribution of measured acute and chronic ecotoxicity endpoints for human medicines in standard studies**



**GRAPH A ACUTE DATA**



**GRAPH B CHRONIC DATA**

**LC50** – concentration of compound that causes 50% mortality in the study

**EC50** – concentration of compound that causes 50% effect (e.g. reduction in growth or reproduction)

The data were taken from the published literature. The data show that generally, algal species are more sensitive in acute studies than fish and daphnia whereas in chronic studies, fish are the most sensitive. The effect concentrations are significantly higher than concentrations of pharmaceuticals seen in the environment indicating that pharmaceuticals will not be at a high enough level in the environment to elicit the effects that were assessed.

### 7.1.2 Non-standard effects

Pharmaceuticals compounds are either designed to be highly active and interact with receptors in humans and animals or they are toxic towards health threatening organisms such as bacteria, fungi and parasites. Many lower animals have receptor systems similar to humans and animals moreover many of the groups of organisms that affect human and animal health and which are targeted by pharmaceuticals play a critical role in the functioning of ecosystems. It is therefore possible that pharmaceuticals may cause subtle effects on aquatic and terrestrial organisms that might not be picked up in the standard studies discussed above.

For human medicines in particular, releases to the environment are likely to be almost continuous so organisms will be exposed for much longer durations than those used in standard tests. Because of this, researchers have begun to investigate some of the more subtle effects caused by long-term low-level exposure to pharmaceuticals. A wide range of subtle impacts have been reported so far (Table 3) including effects on oocytes and testicular maturation; impacts on insect physiology and behaviour; effects on dung decomposition; inhibition or stimulation of growth in aquatic plant and algae species; and the development of antibacterial resistance in microbes. Whilst, many of these effects have been seen at environmentally-realistic concentrations, the significance in terms of environmental health has yet to be established – this will be one of the challenges in the coming years.

More detail of some of the non-standard impacts of pharmaceuticals is given in the following sections.

**Table 3. Reported non-standard effects of human and veterinary medicines on aquatic and terrestrial organisms**

Medicine class	Reported effect	Reference
Anorexic treatments	Hormonal effect in crabs and crayfish	Reported in Daughton and Ternes, 1999
Estrogens	Endocrine disrupting effects on fish	
Parasiticides	Effects on insect development and physiology; Effect on rate of dung decomposition	Floate <i>et al.</i> , (2005); Sommer and Bibby (2002)
Antibacterials	Selection of antibacterial resistance; Impacts on the structure of soil microbial communities; Inhibition of growth blue-green algae and aquatic plants; Biochemical effects in fish	Sengelov <i>et al.</i> , (2003); Pomati <i>et al.</i> , (2004); Westergaard, <i>et al.</i> , (2001); Lavelle <i>et al.</i> , (2004)
Anti-inflammatory	Stimulation of growth of blue green algae and inhibition of growth of aquatic plants; Effects on structure of fish hepatocytes	Pomati <i>et al.</i> , 2004
Lipid regulator	Biochemical effects in fish	Lavelle <i>et al.</i> , 2004
Analgesic	Biochemical effects in fish	Lavelle <i>et al.</i> , 2004
Beta blocker	Biochemical effects in fish	Lavelle <i>et al.</i> , 2004
Lipid regulator	Biochemical effects in fish	Lavelle <i>et al.</i> , 2004
Antianxiety drug	Effects on development of invertebrates	Pascoe <i>et al.</i> , 2003
Cardiac glycoside	Effects on development of invertebrates	Pascoe <i>et al.</i> , 2003
Calcium channel blocker	Effects on development of invertebrates	Pascoe <i>et al.</i> , 2003

Source: Author, see References.

### **Avermectins and terrestrial and aquatic invertebrates**

The avermectins are powerful insecticides. Exposure to avermectins can elicit a number of responses, including adult and larval mortality, an effect on feeding, disruption of water balance, a reduction in growth rate, interference with moulting, inhibition of metamorphosis and/or pupation, prevention of adult emergence, disruption of mating and interference with egg production and oviposition (Floate *et al.*, 2006). As a consequence, dung from animals treated with avermectins may not support the development of either target insects (e.g. *Haemotobia irritans*, *Musca autumnalis*, *Musca domestica* and *Musca vetustissima*) or non-target (e.g. sphaerocerids, muscids, sepsids and coleopterans) insects (Floate *et al.*, 2006). The toxicity of avermectins to dung insect populations may be associated with retardation in the rate of breakdown of pats. For example pats containing ivermectin have been shown to be intact after 340 days, whereas, untreated pats were largely degraded within 80 days (e.g. Floate, 1998).

The effects on other invertebrates have not been extensively investigated although investigations with worms demonstrated no effect on population density (Floate *et al.*, 2006). The possible indirect effects of avermectin contaminated dung on vertebrate populations (e.g. bats and birds) have also been highlighted (e.g. Floate *et al.*, 2006). Their use may result in depletion in the quantity and quality of vertebrate food resources, this may be particularly critical during the breeding season or when young animals are foraging and fending for themselves.



## **Hormones and aquatic wildlife**

Livestock waste manure may be a significant source of hormones, including steroid estrogens such as estradiol, estrone and estriol (Hanselman *et al.*, 2003). It is known that very low concentrations (10 – 100 ng/l) of these compounds can cause significant effects on the reproductive biology of fish and amphibians (Oberdorster *et al.*, 2001; Tyler *et al.*, 1998). For example estrone has been shown to induce the egg yolk protein vitellogenin in male fish and to affect testicular growth at 30 ng/l (Panter *et al.*, 1998; 2000).

## **Antibiotics and soil microbes**

Several studies have investigated the effects of antimicrobial substances on microbes in soils and sediment (e.g. Westergaard *et al.*, 2001). Selected substances have been shown to inhibit soil bacteria as well as reducing the hypha length of active moulds. Effects on the microbial composition of soils have also been demonstrated (e.g. Sommer and Bibby, 2002). With the exception of a few studies (e.g. Sommer and Bibby, 2002), effects on soil and sediment functioning have not been considered. Those studies that have been performed demonstrate that veterinary antibacterials may affect sulfate reduction in soil and that they inhibit the decomposition of dung organic matter in soil (e.g. Sommer and Bibby, 2005). A few studies have also investigated the potential for antibiotics that are excreted by animals to select for antibiotic resistance. For example, Heuer and Schmalla (2007) investigated the effects of pig manure and sulfadiazine on bacterial communities in soil microcosms using two soil types. In both soils, manure and sulfadiazine positively affected the quotients of total and sulfadiazine-resistant culturable bacteria. The results suggest that manure from treated pigs enhances spread of antibiotic resistances in soil bacterial communities. A few studies have also explored effects of veterinary antibiotics on aquatic microbes. Schallenberg and Armstrong (2004) explored the impacts of filtered water from an agricultural drain on lake bacteria. They showed that the drainage water reduced the abundance of aquatic bacteria in a shallow coastal lake and the data indicated that these effects may be due to antibiotics. Finally, in a recent study (Monteiro and Boxall, in press), explored the indirect effects of veterinary antibiotics were explored. In this study, the effects of sulfamethoxazole on the degradation of a range of human medicines in soil were explored. Data for the non-steroidal anti-inflammatory drug, naproxen indicated that the addition of sulfamethoxazole significantly reduced the rate of degradation of the human drug. This observation may have serious implications for the risks of other compounds that are applied to the soil environment such as pesticides.

## **Diclofenac and vultures**

The veterinary use of the non-steroidal anti-inflammatory drug diclofenac was found to be responsible for the decline in populations of three vulture species in Asia (Oaks *et al.*, 2004). The decline in the populations was caused by renal failure and visceral gout which attributed to the veterinary use of diclofenac in cattle. The decline in vulture populations, arising from the use of diclofenac, is thought to have serious implications for human health. As vultures are a keystone species, their population decline has a range of ecological, socio-economic, cultural and human health impacts.

For example, Markandya *et al.* (2008) reviewed the economic implications of the human health impacts of the decline in vulture populations. Livestock carcasses are the main food source for vultures but are also eaten by dogs. As that vulture populations have declined, the dog populations have increased. As dogs are the main source of rabies in humans in India, it is probable that the

incidence of rabies in humans has increased and hence mortality has increased. Markandya *et al.* (2008) estimated that if the vulture decline had likely caused many thousand extra deaths in the human population.

Effects of pharmaceuticals on wildlife may be a broader issue. In a recent study, residues of fluoroquinolone antibiotics have been detected in eggs of vultures and red kites in Spain and the presence of these residues have been associated with fatal embryo chondral damage (Lemus *et al.*, 2009). One reason why top predators may be particularly sensitive to the effects of a pharmaceutical is that many do not possess the detoxification enzymes which are present in (and which protect) the human population.

#### 7.1.3 *Human health effects of human and veterinary medicines*

Humans and top predators may be exposed to pharmaceuticals in the environment by a number of routes including the consumption of: 1) plants that have accumulated substances from soils as a result of exposure to contaminated sludge, manure, irrigation water and slurry; 2) livestock that have accumulated veterinary medicines through the food chain; 3) fish exposed to pharmaceuticals released to surface waters either intentionally (aquaculture treatments) or unintentionally; 4) abstracted groundwater and surface waters containing residues of pharmaceuticals that is then used for drinking water; and 5) for top predators, contaminated food sources such as insects and other invertebrates and other wildlife species. Exposure may also occur via the inhalation of dust emitted from intensively reared livestock facilities (Hamscher *et al.*, 2001).

While, measured and predicted concentrations of pharmaceuticals in drinking water, crops and fish are likely to result in exposure levels that are well below human Therapeutic Dose Levels or Acceptable Daily Intakes (ADIs) (e.g. Cunningham *et al.*, 2009; Webb *et al.*, 2003; Boxall *et al.*, 2006; Watts *et al.*, 2007; Brooks *et al.*, 2005; Ramirez *et al.*, 2009; Hughes *et al.*, 2006; Schwab *et al.*, 2005; Hughes *et al.*, 2006), there is concern from the scientific and regulatory communities and the general public that exposure to pharmaceuticals in the environment may be affecting human health. These concerns arise from the fact that:

The exposure, even though at low levels, is likely to be long-term:

- Individual pharmaceuticals do not occur in drinking water on their own but occur as a mixture, which introduces the possibility of synergistic or additive interactions or environmental contraindications between an environmental residue and a medicine taken by a patient for an existing condition;
- Humans will be exposed to pharmaceuticals via a number of routes, whereas, most risk-assessment studies have only considered one route of exposure;
- Degradation processes, particularly in drinking water treatment processes, may result in transformation products that may be of greater health concern than the parent compound. For example, some pharmaceuticals with amine functionality are possible precursors for nitrosamines – which can be mutagenic and carcinogenic (Krasner, 2009).
- Some compounds, e.g. selected cytotoxic compounds, are known to be extremely potent so it has been recognised that environmental exposure to these should receive special attention (Rowney *et al.*, 2009).
- Indirect effects of residues in the environment, such as the selection of antibiotic resistant micro-organisms, cannot currently be ruled out (Witte *et al.*, 1998; Boxall *et al.*, 2003; Heuer and Schmalla, 2007; Byrne-Bailey *et al.*, 2009)

There is therefore a need to better understand the potential implications of residues of human and veterinary medicines in the environment on the health of humans and other top predators so that pharmaceuticals can be used in a sustainable way and so that public confidence in the safety of food and drinking water can be maintained. It is important to recognise that pharmaceuticals (particularly human medicines) are the most extensively studied group of compounds in terms of human toxicology so much of the data needed to determine risks to humans and other top predators already exist (e.g. data from rat and dog studies on fluoroquinolones show similar effects as seen in vultures and red kites in the wild (Lemus *et al.*, 2009) and, if the exposure pathway had been anticipated, the impacts of diclofenac could have been predictable based on adverse response data for the drug).

## **7.2      *Engineered nanomaterials***

While data are not yet available on the environmental effects of nanopesticides, data are becoming increasingly available on many of the engineered nanomaterials that might be released to the agricultural environment associated with sewage sludge (such as nanosilver, titanium dioxide and fullerenes). Studies have explored the uptake and effects of nanomaterials on a range of environmental species and endpoints (Oberdorster, 2004; Lovern and Klaper, 2006; Oberdorster *et al.*, 2006; Kashiwada, 2006). In the laboratory, aquatic organisms appear to rapidly accumulate selected nanomaterials, including carbon black, titanium dioxide and polystyrene (e.g. Lubick, 2006; Stone *et al.*, 2006).

Laboratory studies with microbes have reported effects of fullerenes on microbial physiology (e.g. Fortner *et al.*, 2005, Fang *et al.*, 2007) whilst silver nanoparticles have been shown to accumulate in bacterial membranes, ultimately causing cell death (Sondi and Salopek-Sondi, 2004). In some cases there is however a mismatch between laboratory studies and studies to assess impacts in the real environment. For example, under realistic exposure conditions, fullerenes have little impact on the structure and function of the soil microbial communities and microbial processes (Tong *et al.*, 2007).

The available data indicate that nanomaterials have low acute toxicity to aquatic organisms (e.g. Lovern and Klaper, 2006; Oberdorster *et al.*, 2006; Zhu *et al.*, 2006) although they may cause oxidative stress and affect the physiology and reproduction (Lovern and Klaper, 2006; Oberdorster *et al.*, 2006; Templeton *et al.*, 2006). Studies with algae have demonstrated that titanium dioxide nanoparticles inhibit algal photosynthesis (Kim and Lee, 2005). Studies with fish have demonstrated oxidative stress in the brains of fish exposed to fullerenes at very low concentrations (Oberdorster, 2004). Although there is some debate over whether the effects were caused by the fullerenes or the carrier solvent. Studies with plants have shown alumina nanoparticles loaded with phenanthrene to inhibit plant growth (Yang and Watts, 2005).

The factors and processes affecting ecotoxicity seem to be complex. The impacts of nanomaterials on environmental organisms seems to be determined by a range of characteristics including dissolution potential, aggregation potential, particle surface properties and the characteristics of the exposure environment and the biochemical, physiological and behavioural traits of the organism of interest (e.g. Dhawan *et al.*, 2006, Rogers *et al.*, 2007). In the future, therefore we need to bring the exposure and effects studies closer together in order to determine whether nanomaterials can pose a risk to the environment (Tiede *et al.*, 2008; SCENIHR, 2007).

## **7.3      *Transformation products***

Data have been generated on the ecotoxicity of pesticide, veterinary medicine and biocide degradates because of the requirement of regulatory schemes (e.g. the EU pesticide directive 91/414/EEC requires that all major degradates formed at >10% of the applied parent compound are

evaluated). Generally, these studies have determined acute effects on organisms used in standard toxicity tests (e.g. daphnids, rainbow trout, earthworms) – the reason being that for the vast majority of pesticide metabolites, the acute package demonstrates no risks, so no further testing is triggered. A few studies have however assessed sublethal and longer term effects (e.g. Osano *et al.*, 2002a and b). The impacts (both acute and longer-term) of a few industrial substances have also been investigated, most notably degradates of the non-ionic surfactants (nonylphenol mono- and diethoxylates, nonylphenol carboxylates, nonylphenol ethoxycarboxylates and nonylphenol itself). These substances are believed to have oestrogenic activity due to their ability to mimic the endogenous hormone 17 $\beta$ -estradiol (Jobling *et al.*, 1996).

The available data demonstrate that in most cases degradates have similar toxicity to or are less toxic than their parents (Grasso *et al.*, 2002, Sinclair and Boxall, 2003). However there are instances where degradates can be more toxic (Box 3). For example, of the degradates investigated by Sinclair and Boxall (2003), 41% were less toxic than their parent, 39% had a similar toxicity to their parent (to account for interlaboratory differences it was assumed that EC50 values within a factor of 3 indicate similar toxicity), 20% of degradates were more than three times more toxic and some degradates (9%) were more than an order of magnitude more toxic. In general, increases in toxicity from parent to degradate were observed for parent compounds that had a low toxicity.

#### **7.4 Mixtures**

It is important to recognise that the environment will not be exposed to single ECs but will be exposed to a mixture of ECs and other contaminants. There is strong evidence from the literature that compounds with a similar mode of action work together to create effects greater than caused by each component of the mixture applied singularly (Kortenkamp *et al.*, 2009). Fewer data are available on the ecotoxicity of mixtures of compounds with dissimilar mode of action but where the data are available, they indicate that these mixtures also cause effects greater than seen for the single substances. It is therefore important that combination effects of ECs and ECs and other contaminants are considered in the future.

Modelling approaches are available for estimating the combined effects of chemicals, namely the Concentration Addition model and the Independent Action model. Through laboratory-based studies, these models have been shown to provide reasonable estimations of combination effects (Kortenkamp *et al.*, 2009). It may be possible to use these models in the risk assessment of EC's.

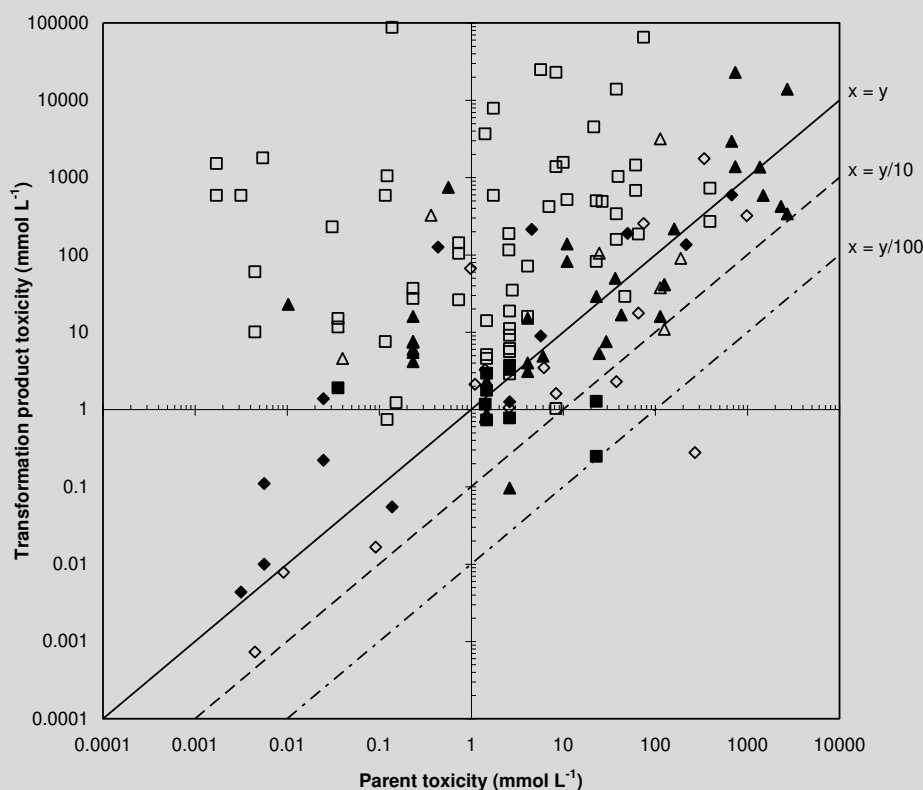
ECs may also affect organisms indirectly through interactions. For example there is concern that nanomaterials can act as carriers for other contaminants into aquatic organisms. This interactive effect was observed in combination studies with fullerene nanoparticles and polycyclic aromatic hydrocarbons. In these studies, the presence of fullerenes increased the rate and extent of uptake of phenanthrene in daphnids. Studies have also shown that the presence of antibiotics in the environment may affect the persistence of other contaminants (Monteiro and Boxall, 2009).

The issue of mixture interactions is not specific to ECs but is a general problem that is relevant to all contaminants in the natural environment.

### Box 6. Comparison of effects data for parent compounds and their associated transformation products

The graph shows the relationship between the ecotoxicity (to fish, daphnids and algae) of parent compounds and their transformation products. All of the points that fall above the solid line ( $x=y$ ) correspond to transformation products that are less toxic than their parent compound. Points below the line correspond to transformation products that are more toxic than the parent, those below the line  $x=y/10$  are more than 10 x more toxic and those below the line  $x=y/100$  are more than 100 x more toxic.

There are a number of possible explanations for these toxicity increases: 1) The active moiety of the parent compound is still present in the transformation product (black diamonds); 2) The transformation product is the active component of a pro-compound (white diamonds); 3) The bioconcentration factor for the transformation product is greater than the parent (black and white triangles); and 4) the transformation pathway results in a compound with a different and more potent mode of action than the parent (white squares) (Sinclair and Boxall, 2003).



## 8. Regulations and policy instruments

The environmental impacts of a number of classes of ECs are captured by existing regulations and policy instruments. These are described below.

### 8.1 Veterinary medicines

Manufacturers of veterinary medicines are required to demonstrate the quality, safety, and efficacy of a new product before it can be marketed. In the United States the regulatory authority is the U.S. Food and Drug Administration. The equivalent authority in the European Union is the European

Medicines Evaluation Agency (EMA) for Europe-wide authorization or Member State regulatory authorities if individual country authorization is sought. In Canada the competent authority is Health Canada, and in Australia it is the Australian Pesticides and Veterinary Medicines Authority.

Historically, individual authorities have had their own guidelines for assessing the risks of a veterinary product. The Veterinary International Co-operation on Harmonisation (VICH) was officially launched in April 1996 to harmonize technical requirements for veterinary product registration across the United States, Canada, Australia, Japan, and Europe. Its members include representatives from government agencies and industry. VICH currently has working groups drafting recommendations in a number of areas including ecotoxicity, safety, efficacy, and pharmacovigilance. The ecotoxicity working group has developed a two-phase approach for use in the registration process.

In the Phase 1 assessment (VICH, 2000) the potential for environmental exposure is assessed on the basis of the intended use of the product. Generally, it is assumed that products with limited use and limited exposure have limited effects and for these products assessment stops at Phase 1 (i.e., they do not require a Phase 2 assessment). The exceptions to this are products for which there are specific concerns over activity and use. These automatically require a Phase 2 assessment regardless of the potential extent of exposure.

In Phase 2, a two-tiered approach is used to assess the environmental risks of products that identified in Phase I as being of potential risk to the environment (VICH, 2006). Tier A makes use of less expensive ecotoxicity and fate studies to make a conservative assessment of risk in the environmental compartment of interest. If a product cannot be shown to pose an acceptable risk using these data, then the risk assessment is refined in Tier B.

## **8.2      *Human medicines***

In the EU and the US, guidelines are also available for the environmental risk assessment of human pharmaceuticals. The current guidance document, adopted by the EMA Committee for Human Medicinal Products, came into effect in the end of 2006. An Environmental Risk Assessment (ERA) is required for all new marketing authorisation applications for medicinal products, for type II variations (major changes to the marketing authorisation) and for extension applications if there is an increase in environmental exposure. The ERA is performed in 2 phases. In Phase I, the concentration of the drug in the aquatic environment is calculated. If the PEC is below 10 ng/l, then it is assumed that the substance will pose a low risk to the environment, unless it is a substance the effects reproduction of vertebrates or lower animals. If the PEC is above 10 ng/l, then a Phase 2 assessment is required. Phase 2 is a two phase process and in phase 1 the fate and effects (i.e. algal growth study, Daphnia reproduction study, and fish early life stage study) of the compound in the aquatic environment are assessed. In tier B, extended effects analysis studies may be performed and if the Koc of the compound is > 10,000 then risks to the terrestrial environment, arising from sludge application to land, also need to be considered. Unlike veterinary medicines, a marketing authorisation for a human pharmaceutical will not be refused based on the ERA.

## **8.3      *Transformation products***

The environmental risks of transformation products have to be considered for many classes of chemicals. For example, the pesticides directive (2009/1107) requires assessment of major transformation products and relevant transformation products of plant protection products. Similar requirements also exist for transformation products of pesticides in other geographical locations (e.g. FIFRA in the USA), biocides and human and veterinary medicines.

#### 8.4 *Nanomaterials*

As engineered nanomaterials are expected to be used in a wide range of product types, it is likely that a range of environmental regulatory frameworks will apply to them. For example, industrial uses are likely to be covered by the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulations, whereas applications in the pharmaceutical, biocides, veterinary medicines and plant protection products will be covered by other specific frameworks (e.g. Aitken *et al.*, 2006).

#### 8.5 *Other regulatory frameworks*

Many ECs, that are not covered by the mechanisms described above, are likely to be covered by the recent EU Regulation (EC) No. 1907/2006, the REACH Regulations, which entered into force on June 1, 2007. REACH will require an environmental safety assessment of all chemicals used or imported into the EU in quantities exceeding one tonne. The Water Framework Directive and the new European soils policy may also influence the management of ECs in the natural environment.

### 9. *Risk mitigation*

In the event that an EC is identified as posing an unacceptable risk to the environment, there are a number of options that exist for managing or mitigating the risks. For example, over recent years there has been a steadily increasing drive within the pharmaceutical industry towards the synthesis of 'greener' pharmaceuticals and the adoption of green chemistry methods and technologies (Clark *et al.*, 2008). The majority of improvements have been made to the manufacturing process, although increasing emphasis is being placed on the development of approaches for minimising impacts during use including the development of more efficient wastewater treatment technologies, and development of pharmaceuticals that are benign by design or designed for biodegradability (Clark *et al.*, 2008). The implementation of tax and other incentives could make these eco-pharmacostewardship approaches more attractive to pharmaceutical companies and hence increase their uptake.

Classification and labelling approaches may also help to minimise risks. A good example of such a scheme is a system running in Sweden which is a voluntary scheme that targets active pharmaceutical substances where information on their environmental impacts is made publicly available on websites and in information booklet (Stockholms Läns landsting, 2006). The extension of a model similar to the Swedish scheme could potentially be desirable on a European level. Key issues for developing and implementing classification & labelling schemes include the standardisation of the information used, the criteria applied, who provides the information and mode of communication (Clark *et al.*, 2008).

In Europe, drug take back schemes of unused/expired medication are an obligatory post-pharmacy stewardship approach that reduces the discharge of pharmaceuticals into environmental waters and minimises the amounts of pharmaceuticals entering landfill sites. Although the contribution of improper disposal of pharmaceuticals to the overall environmental burden is generally believed to be minor (Daughton and Ruhoy, 2009), drug take back schemes are still considered to be important. High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs are key for the success of such schemes.

Changes in agricultural practices may also minimise the risks of ECs to the environment. A range of approaches can be used including changes in treatment timings and intensities, changes in manure/sludge application rates and timings, development of recommendations on when not to apply manure and biosolids (e.g. where slopes are unsuitable), and specification of buffer zones can protect water bodies (Pope *et al.*, 2009). For example, injection application has been shown to reduce

overland runoff of pharmaceuticals and personal care products when compared to a broadcast application (Topp *et al.*, 2008). The timing of application might also minimize the risk of contamination. For example, the application of sewage sludge during dry periods would minimise the potential for some substances to be transported to surface waters.

## **10. Environmental risks of ECs in the future**

It is also important to recognize new contaminants will emerge in the future due to a range of drivers including: demographic change; changes in land use; changes in waste disposal practices (e.g. moving to composting and anaerobic digestion approaches with subsequent application of the compost, digestate etc. to land); and global climate change. A recent study (Boxall *et al.*, 2009) explored the potential impacts of climate change on the risks of contaminants in agricultural systems, focusing on the UK environment. The study concluded that climate change is likely to impact the dispersion of chemicals in the environment (Figure 4). In addition changes in climate are likely to affect the amounts and types of chemical used for in agriculture. Future risks of chemicals could therefore be very different than today so it is important that we begin to assess the implications of climate change for changes in environmental and human exposures to chemicals and the subsequent impacts in the near term and in the future. Based on the work, overall it is anticipated that climate change will result in an increase in risks of chemicals from agriculture to environmental and human health. The magnitude of the increases will be highly dependent on the contaminant type. Climate change will fuel increased use of pesticides and biocides as farming practices intensify. Extreme weather events will mobilise contaminants from soils and faecal matter, potentially increasing their bioavailability. Climate change will also affect the fate and transport of chemical contaminants in agricultural systems. Increases in temperature and changes in moisture content are likely to reduce the persistence of chemicals while changes in hydrological characteristics are likely to increase the potential for contaminants to be transported to water supplies. Risks of many particulate and particle-associated contaminants could therefore increase significantly. The study concluded that it should be possible to manage many of these risk increases through better regulation, monitoring and the development of long-term research programmes.

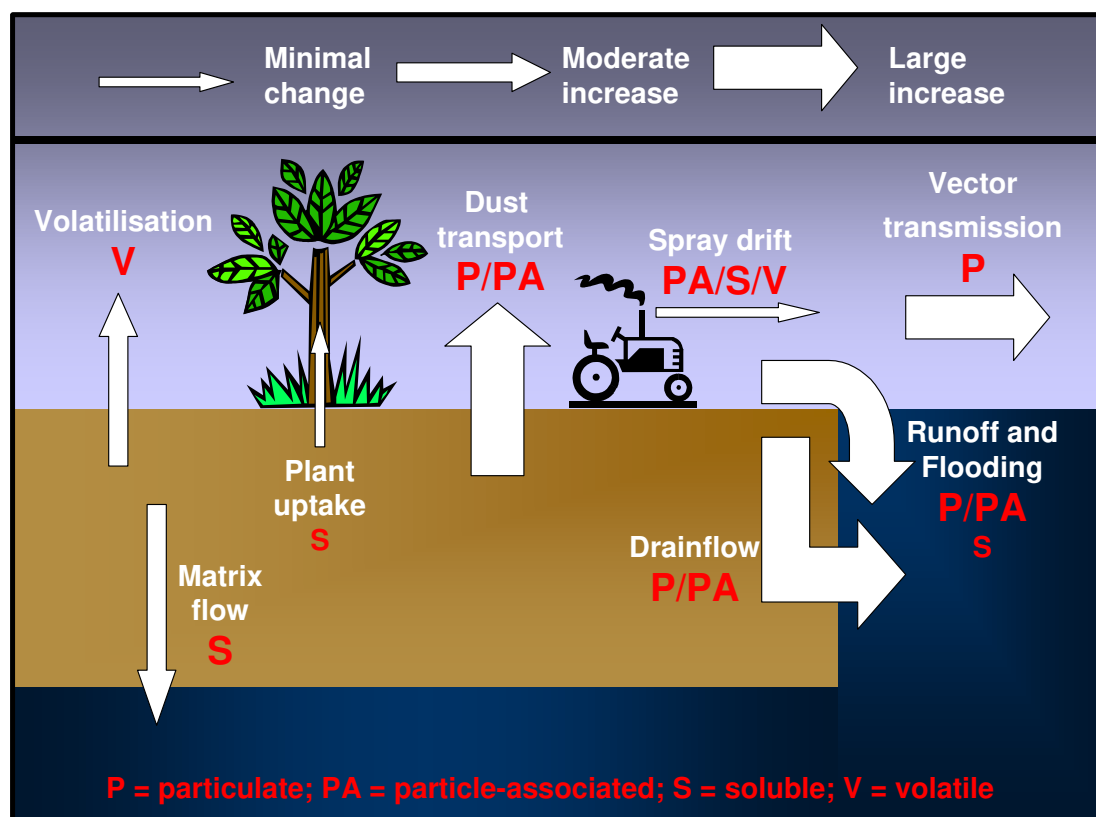
## **11. How can policy makers identify emerging contaminants of most concern?**

It is clear from the above that a wide range of ECs will be released to the environment and that the nature of the ECs released to the environment will vary both temporally and spatially. We probably do not have the resources to experimentally assess the risks of every potential EC and there is therefore an urgent need for approaches that can be applied by environmental agencies and/or policy makers within a particular region to identify ECs of most concern. These ECs would then be the focus of monitoring investigations and fate and effects studies. Over the past few years there has been increasing interest in the development of prioritization approaches for identifying ECs of most concern. In this Section a number of these approaches that have been used for agricultural ECs are described.

A number of previous studies have been performed to identify priority emerging environmental pollutants (e.g. Boxall *et al.*, 2003; Thomas *et al.*, 2004; Capelton *et al.*, 2006; Sinclair *et al.*, 2006; Sanderson *et al.*, 2003; Table 3). These have considered a range of classes (veterinary and human medicines and degradates), different exposure pathways and have been aimed at different protection goals (selected priority lists of relevance to agricultural systems are given in Appendix A).



**Figure 4. Predicted impacts of climate change on transport processes for contaminants in agricultural systems**



The size of the arrow indicates the magnitude of change in the transport pathway. The letters indicate the types of contaminant that will be transported by the pathway (P = particles, PA = particle associated; S = soluble; V = volatile). The size of the letter indicates that importance of the pathway for that contaminant type.

Source: Taken from Boxall *et al.* (2009).

**Table 4. Previous horizon scanning studies for emerging environmental contaminants**

Study	Emerging contaminant class	Protection goal	Exposure pathways	Parameters
Boxall <i>et al.</i> , 2003	Veterinary medicines	Environmental	Soil, Surface water	Usage, Ecotoxicity
Thomas <i>et al.</i> , 2004	Human medicines	Environmental	Surface water	Usage, Ecotoxicity, Therapeutic dose
Capelton <i>et al.</i> , 2006	Veterinary medicines	Human	Drinking water, Vegetables, Meat, Fish	Usage, Toxicity
Sinclair <i>et al.</i> , 2006	Transformation products	Human	Drinking water	Usage, Sorption, Persistence, Toxicity
Sanderson <i>et al.</i> , 2003	Human medicines	Environmental		Usage, Exposure, Ecotoxicity
Eljarrat and Barcelo, 2003	Emerging persistent organic pollutants (e.g. dioxin-like compounds)	Human	Sediments, sludge	Chemical analysis, toxicity

Most of these approaches integrate data on the potential hazard of an EC to either organisms in the environment or to human health and combine this with estimates of exposure. As no experimental data are available on the ecotoxicity and environmental properties of most ECs, the prioritization approaches that have been used are very reliant on modelling predictions of fate and effects data. As stated in Section 4, many of the modelling approaches that are available for estimating fate properties and exposure are not necessarily appropriate for many classes of ECs so the priority lists should be viewed with some caution. By developing new or improved models for assessing the fate and effects of ECs and integrating these into prioritisation schemes, it should be possible in the future to identify ECs of most concern and to focus testing requirements. The prioritisation approaches have also focused on single compounds and interactions of ECs have not been considered.

## 12. Knowledge gaps and research needs

From the previous sections, it is clear that over the last few years that there has been increasing interest in the risks of emerging contaminants in the environment and there are also examples where ECs have caused catastrophic impacts on ecosystems (e.g. the effects of diclofenac and vultures). It is therefore critical that we continue to work to identify ECs of most concern in a logical and pragmatic manner. In order to do this, there are many questions that need to be addressed:

- What are the risks of substances that have yet to be studied? – Due to resource limitations only a small proportion of substances in use today have been investigated. There is therefore a need to develop an understanding of how other substances will affect the environment and for the further development of approaches for identifying substances of most concern.
- How can we analyse certain emerging contaminants in environmental media? – While there have been significant advances in analytical technology over the last decade which now allows us to detect many classes of emerging contaminants at low levels in complex media, for selected contaminants (e.g. engineered nanomaterials), method development is still in its infancy (e.g. Tiede *et al.*, 2008).
- Are we considering all the main exposure pathways? – Current regulatory environmental risk assessment approaches for assessing exposure to ECs focus on leaching to groundwater and runoff to surface waters from soils. It is possible that important exposure pathways are being missed and it is also likely that different exposure pathways will vary in importance from one geographical location to another. There is a real need to identify all the potential pathways of exposure of environmental organisms to ECs that occur across the globe and, where appropriate, to develop models to cope with additional pathways.
- How can we better assess ecotoxicity? It is possible that current standard ecotoxicity tests may not always catch the impacts of selected emerging contaminants (e.g. pharmaceutical effects on birds). The use of more subtle endpoints such as impacts on behaviour, physiology and biochemistry might help as could ‘read across’ approaches from mammalian toxicology and pharmacology studies to environmental organisms.
- How will ECs interact with a) each other; and b) other contaminants? – The environment will be exposed to a mixture of ECs and other contaminants. The combined effects of these mixtures are likely to be greater than the single compounds alone. It is important that we begin to understand how ECs interact with each other and with other contaminant classes and that methods are developed for identifying the implications of these interactions in terms of risk to the environment. These studies should not only focus on toxicant-toxicant interactions but also interactions which have an indirect impact on risk.

- What do the ecotoxicity data mean? – A number of subtle effects have been demonstrated following exposure to selected emerging contaminants at environmentally realistic concentrations. We need to establish what these data mean, if anything, in terms of effects on ecosystem functioning.
- What are the mechanisms determining and fate and behaviour of emerging contaminants? – For many traditional contaminants, our understanding of those factors and processes affecting fate and behaviour in the environment is well developed and models are available for predicting a range of important fate parameters (e.g. sorption, bioaccumulation). However, for many emerging chemical contaminant classes, other fate mechanisms appear to be important. In the future we need to try and further understand these mechanisms in order to develop improved models for use in environmental risk assessment. Additionally we need to better understand the effects of manure, sludge and waste matrices on contaminant behaviour in agricultural systems.
- How can we mitigate against any identified risks? – In the event that a risk of an emerging contaminant to the environment is identified, it may be necessary to introduce treatment and mitigation options. By better understanding those factors controlling the fate and behaviour of different classes of emerging contaminant, we should be better placed to optimise existing remediation technologies or develop new approaches to reduce risks.
- What will agricultural systems look like in the future and how will this effect contaminant risk? – Agricultural systems are likely to look very different in the future due to land use, demographic and climate change. These changes are likely to affect the risks of contaminants in agricultural systems. It is therefore important that we begin to assess how agricultural systems might change in the future and to assess how these changes will affect contaminant inputs, exposure, effects and risks.

## APPENDIX A – PRIORITY LISTS FOR EMERGING CONTAMINANTS IN AGRICULTURAL SYSTEMS

**Table A1. High priority veterinary medicines in terms of potential risk to UK ecosystems**

Compound	Treatment scenario(s) that pose a 'high risk'
amoxicillin	herd and aquaculture
apramycin	herd
chlortetracycline	herd
cypermethrin	herd
diazinon	herd
dihydrostreptomycin	herd
oxytetracycline	herd and aquaculture
sarafloxacin	aquaculture
sulfadiazine	aquaculture
tetracycline	herd
tylosin	herd

Source: Taken from Boxall et al. (2003b).

**Table A2. Priority veterinary medicine active ingredients recommended for further study to assess toxicological risks resulting from human exposure pathways**

Veterinary medicine active ingredient	CAS number	Therapeutic indication	Chemical group	Potential to reach the environment	Usage	Toxicological hazard	Overall priority Level for detailed risk assessment
Albendazole <sup>a</sup>	54965-21-8	Anthelmintic	Benzimidazole	Unknown	Medium <sup>b</sup>	High	High
Amoxicillin <sup>a</sup>	26787-78-0	Antimicrobial	β-lactam	High	High	High	High
Baquioprim <sup>a</sup>	102280-35-3	Antimicrobial	Diaminopyrimidine derivative	Unknown	High	High	High
Chlorhexidine <sup>a</sup>	55-56-1	Antimicrobial and antiseptic	-	High	Low <sup>b</sup>	High	High
Levamisole <sup>a</sup>	14769-73-4	Anthelmintic	Imidazothiazole	High	Medium <sup>b</sup>	High	High
Monensin <sup>a</sup>	17090-79-8	Coccidiostat MFA	-	Unknown	High <sup>b</sup>	High	High
Nitroxynil <sup>a</sup>	1689-89-0	Flukicide	-	Unknown	Medium <sup>b</sup>	High	High
Oxolinic acid	14698-29-4	Antibiotic MFA	Quinolone	High	Medium <sup>b</sup>	High	High
Procaine benzylpenicillin <sup>a, c</sup>	6130-64-9	Antimicrobial	β-lactam	Unknown	High	High	High
Salinomycin sodium <sup>a</sup>	53003-10-4	Coccidiostat MFA	-	Unknown	High <sup>b</sup>	High	High
Sulfadiazine <sup>a</sup>	68-35-7	Antibiotic MFA and antimicrobial	Sulfonamide	High	High	High	High
Toltrazuril <sup>a</sup>	69004-03-1	Coccidiocide	Triazinetrione derivative	High	Low <sup>b</sup>	High	High
Trimethoprim <sup>a</sup>	738-70-5	Antibiotic MFA and antimicrobial	-	High	High	High	High
Altrenogest <sup>a</sup>	850-52-2	Sex hormone	-	Unknown	Low	High	Medium
Bronopol <sup>a</sup>	52-51-7	Antimicrobial	-	High	Unknown	Medium	Medium
Chlortetracycline <sup>a</sup>	57-62-5	Antibiotic MFA and antimicrobial	Tetracycline	High	High	Medium	Medium
Clavulanic acid <sup>a</sup>	58001-44-8	Antimicrobial	-	Unknown	High	Medium	Medium
Deltamethrin <sup>a</sup>	52918-63-5	Ectoparasiticide	Pyrethroid ester	High	Unknown	Medium	Medium

(continued)

**Table A2. (continued) Priority veterinary medicine active ingredients recommended for further study to assess toxicological risks resulting from human exposure pathways**

Veterinary medicine active ingredient	CAS number	Therapeutic indication	Chemical group	Potential to reach the environment	Usage	Toxicological hazard	Overall priority Level for detailed risk assessment
Diazinon <sup>a</sup>	333-41-5	Ectoparasiticide	Organothiophosphate	High	High	Medium	Medium
Dihydrostreptomycin <sup>a</sup>	128-46-1	Antimicrobial	Aminoglycoside	High	High	Medium	Medium
Emamectin benzoate <sup>a</sup>	137512-74-4	Ectoparasiticide	Avermectin	High	Unknown	Medium	Medium
Florfenicol <sup>a</sup>	73231-34-2	Antibiotic MFA and antimicrobial	-	High	Medium <sup>b</sup>	Medium	Medium
Flumethrin	69770-45-2	Ectoparasiticide	Pyrethroid ester	High	Medium	High	Medium
Mebendazole <sup>a</sup>	31431-39-7	Anthelmintic	Benzimidazole	Unknown	Medium <sup>b</sup>	Medium	Medium
Medroxyprogesterone <sup>a</sup>	520-85-4	Sex hormone	-	Unknown	Low	High	Medium
Oxytetracycline <sup>a</sup>	79-57-2	Antibiotic MFA and antimicrobial	Tetracycline	High	High	Medium	Medium
Procaine hydrochloride	59-46-1	Neurological preparation	Amino ester	Unknown	Medium <sup>b</sup>	Medium	Medium
Sarafloxacin	98105-99-8	Antibiotic MFA	Fluoroquinolone	High	Low	High	Medium
Tetracycline <sup>a</sup>	60-54-8	Antimicrobial	Tetracycline	High	High	Medium	Medium
Tylosin <sup>a</sup>	1401-69-0	Antibiotic MFA and antimicrobial	Macrolide	High	High	Medium	Medium

Source: Taken from Capleton *et al.* (2006)

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